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Date: 6/1/2009
Craig Byrnes**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re patent application of:

Applicant: Hedding-Eckerich, et al.

Examiner: Patrick Lewis

Serial No: 10/511,026

Art Unit: 1623

Filing Date: May 31, 2005

Title: USE OF PYRIMIDINE NUCLEOTIDES FOR THE TREATMENT OF
AFFECTIONS OF THE PERIPHERAL NERVOUS SYSTEM

Mail Stop Appeal Brief – Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY BRIEF

Dear Sir:

Appellants' representative submits this Reply Brief in response to the Examiner's Answer dated March 30, 2009 and in connection with an appeal of the above-identified patent application. Since May 30, 2009 is a Saturday, this Reply is timely filed on the next business day Monday, June 1, 2009.

REMARKS

Claims 1-17 are pending in the application. Favorable reconsideration is respectfully requested in view of the comments herein.

The Obviousness Rejection

Claims 1-17 stand rejected under 35 U.S.C. 103(a) in view of Connolly et al, TIPS (1999), Vol. 20, pgs. 218-225. Connolly generally relates to the use of pyrimidine nucleoside uridine and uridine nucleotides in some human pathophysiological conditions (the only relevant condition being diabetic neuropathy). The Examiner's contentions rely primarily upon Connolly reference number 31, Gallai et al (Acta Neurol. Scand., Vol. 86, pgs. 3-7). Gallai relates to sole use of uridine nucleoside as a treatment for diabetic peripheral neuropathy.

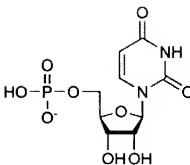
The Examiner asserts that Connolly teaches a method of using nucleotides uridine-5'-monophosphate or cytidine-5'-monophosphate (UMP or CMP respectively) for the treatment of affections of the peripheral nervous system and/or for the stimulation of the regeneration of nerves comprising administering UMP or CMP to a patient in need thereof. The Examiner contends that the few studies of the effects of uridine and uridine nucleotides on the isolated tissues from the nervous system have concentrated mainly on the peripheral nervous system, and that uridine dramatically promoted recovery from degeneration produced by diabetic neuropathy (Connolly, Table 1, ref. 31). The Examiner also contends that since the group consisting of uridine, UMP, UDP, and UTP is a small number of compounds, that the use of UMP would have been readily envisioned by a person having ordinary skill in the art (Examiner's Answer, pg. 5). It is respectfully requested that the Examiner's rejection be withdrawn for at least the following reason; the Examiner appears to rely on an "obvious to try" argument with specific respect to the compound UMP or CMP. A person having ordinary skill in the art simply would have had no motivation to try UMP or CMP based upon the little available knowledge of abnormal nucleotide metabolism in diabetic neuropathy.

An argument of "obvious to try" is impermissible in situations that involve the exploration of "a new technology or general approach that seemed to be a promising field of experimentation, where *the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it*". In re Kubin, (Fed. Cir. 2009)(citing In re O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988)) (emphasis added). "KSR affirmed the logical inverse of this statement by stating that § 103 bars patentability unless 'the improvement is more than the predictable use of prior art elements according to their established functions.'" In re Kubin, (Fed. Cir. 2009)(citing KSR v. Teleflex, 550 U.S. 398 at 417 (2007)). In the present case, the Examiner concedes that Connolly teaches therapeutic benefits "broadly" but maintains that the term "uridine", as used in Table 1 is interpreted to mean uridine and its nucleotides (Examiner's Answer, pg. 5). The latter statement is clearly not the case because Gallai (Table 1, ref. 31) simply does not teach that uridine is converted to UMP in diabetic neuropathy. Gallai merely discloses the longtime known metabolic pyrimidine salvage pathway as a speculative basis contemplating one possible reason uridine administration over prolonged period shows improvement in some diabetic neuropathy patients. In actuality, Gallai teaches little if anything beyond "[the] efficacy of uridine in the treatment of diabetic neuropathy" (concluding statement). Hence, Connolly does not teach the use of either UMP or CMP, merely the long-term administration of uridine nucleoside for diabetic neuropathy.

It is important to note that uridine and UMP have distinct compositions and structures (as visualized below); and that in normal cellular metabolism, as disclosed in Gallai (Connolly, Table 1, ref. 31), UMP is produced by either *de novo* pyrimidine synthesis or by the pyrimidine salvage pathway. In *de novo* pyrimidine synthesis, UMP is produced by the precursor molecule Orotidine 5'-monophosphate (OMP), not uridine, via a reaction catalyzed by the enzyme OMP decarboxylase (consistent with Connolly Figure 1). Alternatively, under normal cellular physiology, UMP can also be produced via precursor molecule uridine catalyzed by uridine kinase.



Uridine



UMP

However, since Connolly is premised on the notion that **adverse neurological effects occur due to alterations in uridine metabolism**, a person having ordinary skill in the art would certainly not expect the metabolic pathways involving uridine and metabolites to function normally. Consistent with such premise, it is well known from classic studies that uridine kinase activity is decreased in extracts from diabetic rats as compared to the enzyme activity in wildtype control animals, and accordingly that **uridine nucleotide synthesis by the salvage pathway is decreased in experimental diabetes** (see e.g. Gertz and Haugaard, *Metabolism*, Vol. 28(4)(1979): 358-362). Therefore, based upon the teaching of Connolly, a person having skill in the art at the time of invention would not have been motivated to try either nucleotide UMP or CMP for the treatment of affections of the peripheral nervous system and/or for the stimulation of the regeneration of nerves.

It is also important to reiterate that a point of novelty in the pending application is a remarkable and unpredictable result over both the prior art as well as the Examiner's interpretation of Connolly. Although Connolly (via Gallai) reports slight improvements in neuropathy patients over a prolonged period (Connolly, pg. 224, column 2), 4 of 5 parameters in the Gallai study were not statistically significant until after greater than 60-120 days of 300mg uridine nucleoside per day. Contrarily, the subject application teaches that only 19.349mg UMP (corresponding to a mass of 12.834 mg uridine) achieves marked reductions in both patient mobility and patient pain in as early as 24 hours (pg. 6, example; pg. 7, results; and Tables 1 and 2). Therefore, when Connolly is properly read in light of Gallai, it merely teaches that it takes between greater than a 23-

fold higher dose (300mg/12.834mg=23.4) and at least 3-fold the greatest dose UMP or CMP recited in claims 5, 8, and 12-16 (300mg/100mg=3.00) while using a different compound than the subject invention (i.e. uridine), only to achieve inferior results.

Further, it is well known in the art that administration of either single compound UMP or CMP does not elicit profound improvements in the treatment of neuropathy. For instance, the International Preliminary Examination Report and the Information Disclosure Statement both disclose three separate references by Wattig et al. that are explicitly contrary to the Examiner's assertions. Specifically, D1 (Z. Klin. Med. 1991, 46(19), 1371-1373; pg. 1372) clearly teaches that only the combination of UMP and CMP, together, is effective in nerve regeneration; and that **single compounds UMP or CMP are themselves ineffective**. Nevertheless, even if nucleoside uridine affects the bioavailability of UMP in diabetic peripheral neuropathy, the claimed range of UMP or CMP is more effective at doses at least 3-fold lessor than Connolly (via Gallai). Hence, not only does the disclosed cited art teach away from the administration of single nucleotides UMP or CMP;

"A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994);

Connolly neither teaches nor suggests that the bioavailability of either UMP or CMP is altered upon prolonged administration of uridine in cases of peripheral neuropathy.

For at least the above reasons, the claims currently under consideration are believed to be patentable over the cited art. Accordingly, it is respectfully requested that the rejections of claims 1-17 be reversed.

If any additional fees are due in connection with this document, the
Commissioner is authorized to charge those fees to Deposit Account No. 50-1063.

Respectfully submitted,

TUROC & WATSON, LLP

/Greg Turocy/

Gregory Turocy
Reg. No. 36,952

Key Tower, 57th Floor
127 Public Square
Cleveland, Ohio 44114
(216) 696-8730
Fax: (216) 696-8731